DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Michael A. Trapani
Vice President of Regulatory Affairs and Quality Assurance
Cytogen Corporation
600 College Road East
Princeton, New Jersey 08540

Dear Mr. Trapani:

During an inspection of your facility located at 600 College Road East, Princeton, New Jersey, between April 26 and May 13, 1999, our investigators identified the following violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and Title 21, Code of Federal Regulations (21 CFR), Parts 211 and 600-680:

1. Failure to establish appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient for each batch of drug product prior to release [21 CFR 211.165(a)] in that the total radioactivity specifications for releasing OncoScint and ProstaScint have not been established.

2. Failure to assure an adequate system for cleaning and disinfecting aseptic processing areas and equipment [21 CFR 211.42(c)(10)(v)] in that there is no assurance that disinfectant studies were conducted under worst case conditions. The studies used only the organisms that were present in the facility on the day of cleaning.

3. Failure to follow written procedures applicable to the quality control unit [21 CFR 211.22(d)] in that the standard operating procedure (SOP) entitled "Stability and Retention Sample Program for Commercial Biological Products and Their Components"

requires that: (1) Quality Control (QC) forward all stability data completed for a particular time point to Quality Assurance (QA) for auditing within ——— of completion and (2) QA audit stability results within ——— after receipt from QC. This SOP was not followed in that:

a. QC or QA has not reviewed the bulk intermediate stability data for OncoScint, lot C5R0917, at ———. The testing was completed on June 23, 1998; however, as of May 13, 1999, QC and QA had not reviewed and/or audited the results.

b. ProstaScint, lot L6C0964A, failed the——— stability testing for protein content on December 31, 1997. Although QC and QA reviewed and audited the results on January 12 and March 18, 1998, respectively, the test failure was not detected until May 1998.

4. Failure to establish, maintain, or follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100]. For example:

a. The SOP entitled "The Cleaning and Sanitization of ——— or Workstation" states that the disinfectants ——— are to remain in contact with the areas being cleaned for ——— and ——— respectively, prior to removal. However, there is no data demonstrating that organisms are killed after exposure at the specified times.

b. The SOP entitled "Evaluation of Column Performance and Packing Efficiency by ——— Determination" states that if the curren. ——— ——— value differs from the previou: ——— value by greater than —— the column is not well packed and a Supervisor must be notified. The following ——— Columns, which are used in the conjugation process of OncoScint and ProstaScint, did not meet this specification: (1) 121092A tested March 11, 1998, (2) 910218 tested March 12, 1998, and (3) 040792A tested March 18, 1998. There is no documentation that a Supervisor was notified. In addition there is no documentation that an investigation was conducted and corrective action was taken.

5. Failure to establish or follow written procedures for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product [21 CFR 211.67(b)] in that the SOP entitled "Preventative Maintenance and Monitoring of the Water System" was not followed in tha. ——— maintenance for several filters used in the water system was not performed from 1998 to May 1999.

6. Failure to ensure that master production and control records include complete manufacturing and control instructions, sampling and testing procedures, specifications,

special notations, and precautions to be followed [21 CFR 211.186(b)(9)] in that the Master Batch Record #710-0258 (Bulk Conjugate) contains errors. Although the errors were detected in March 1998, the record had not been corrected as of May 1999.

7. Failure to fully investigate a batch that does not meet any of its specifications [21 CFR 211.192]. For example:

   a. Although consumer complaints regarding excessive radioactivity on the filter face after performance of the radiolabeling procedure have been closed, Cytogen Corporation (Cytogen) has not finalized the investigation into the cause of excessive radioactivity adhering to the filter. Cytogen has been receiving complaints for this problem since 1993.

   b. Investigations of consumer complaints since 1993 regarding excessive radioactivity on the filter face have been limited to review of the batch record of the affected lot.

   c. The investigation into a consumer complaint for OncoScint, lot 0990A3, was incomplete. The complaint indicated that the product failed to meet the specified radiochemical purity after three attempts. The investigation report stated that: (1) from available information and (2) because other kits from the same lot were successfully radiolabeled, the reason the product failed to meet its specification could not be determined. However, the report also noted that improper handling of the Instant Thin Layer Chromatography strips could lead to contamination. Cytogen did not investigate this possible cause for the failure.

8. Failure to maintain records of returned drug products including the name and label potency of the drug product dosage form, lot number, reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product [21 CFR 211.204] in that the Return Kit Log from 1997 to 1999 does not include the reasons why 13 ProstaScint kits and 8 OncoScint kits were returned to Cytogen. In addition, there is no indication that these lots and any associated batches were evaluated for product quality complaints.

We acknowledge receipt of your responses dated June 10, July 12 and 23, and August 6, 1999, which address the inspectional observations on the Form FDA-483 issued at the close of the inspection. Please note that the response dated August 6, 1999, will be addressed under separate cover. Corrective actions addressed in your letters may be referenced in your response to this letter, as appropriate; however, your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our evaluation of your response follows, and is numbered to correspond to the items listed on the Form FDA-483:

1a. The response indicated that the SOPs entitled _____ _____ and "Determination of the _____

——— that were submitted for our review now include release specifications for total radioactivity for OncoScint and ProstaScint. Please ensure that procedures address actions to be taken, including investigations, corrective actions, and product disposition, when the total radioactivity of a lot does not meet specifications.

1c. We note that Cytogen has been receiving consumer complaints of excessive radioactivity adhering to the filter since 1993. Please indicate the time frame in which Cytogen will complete the investigation regarding these complaints, and include the corrective actions.

21. The response stated that product is refiltered when the initial filter fails integrity testing. Please ensure that data are available which demonstrate that product quality is not affected by a second filtration. This information will be reviewed at the next inspection.

43b. The response stated that the SOP entitled "Alarm Condition Response" will be revised to include documentation regarding: (1) final QA assessment concerning an alarm condition, including impact to product and (2) the rationale for not convening a Materials Review Board to address any further actions. We note that Section 6.3.2.2 states that several steps will be taken when personnel cannot rectify a problem "within a reasonable time." We recommend that the SOP be revised to specify a maximum time in which product may be exposed to conditions that exceed specified parameters. In addition, for critical control areas and equipment, the length of time a product is exposed to conditions that exceed specified parameters should be documented.

48. The response stated that the SOP entitled ——— will be revised to assign responsibility for changing and testing filters to the ——— Department. We note that Section 6.5.2.1 states that a filter that fails post-use integrity testing may be tested a total of —— times before department manager(s) and QA are notified. Please ensure that SOP(s) contain appropriate justification, investigation, and documentation for repeat testing of filters that fail integrity testing.

Your response stated that Cytogen would ——— which was the practice at the time of this inspection. The response also stated that if Cytogen decided to ——— Form, FDA 483 items ——— would be addressed. Should Cytogen elect to begin ——— we recommend that: (1) ——— and (2) ———

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations. It is your responsibility to ensure that your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and all applicable regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes seizure and/or injunction, license suspension and/or revocation.

You should notify this office in writing, within 15 working days of receipt of this letter, of specific steps you have taken or will take to correct or prevent these deviations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.

Sincerely,

Deborah D. Ralston
Acting Director
Office of Regional Operations